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Original Article

Effect of Electroconvulsive Therapy on Serum Thrombospondin-1 Levels in Serious Mental Disorders

Ciddi Ruhsal Bozukluklarda Elektrokonvülzif Terapinin Serum Trombospondin-1 Düzeylerine Etkisi

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ABSTRACT

Objective: There is growing evidence that electroconvulsive therapy increases the expression of Thrombospondin (TSP)-1 and that its synaptogenic effect is likely related to TSP-1. The aim of this study was to define the role of TSP-1 in the effect of electroconvulsive therapy and to compare the TSP-1 level in serious mental disorders with healthy controls.

Methods: Among male patients who were hospitalized with the diagnosis of bipolar disorder or schizophrenia and referred to the electroconvulsive therapy at hospital, 20 patients with acute episodes of schizophrenia, 10 patients with manic episodes of BD, and 28 gender- and age-matched healthy controls were included in the study.

Results: While serum TSP-1 levels were significantly lower in patient group than in the control group (P=.008), post-electroconvulsive therapy serum TSP-1 levels were not significantly different from the control group (P=.116). There was no statistically significant difference in serum TSP-1 levels between before and after electroconvulsive therapy in the patients (P=.360). No correlation was established between serum concentrations of TSP-1 before and after electroconvulsive therapy and clinical or laboratory results.

Conclusion: Based on the results of our study, significantly lower levels of serum TSP-1 in patients with bipolar disorder and schizophrenia compared to controls and the disappearance of the difference after electroconvulsive therapy suggests that TSP-1 may have a role in the mechanism of action of electroconvulsive therapy.

Keywords: Thrombospondin-1, electroconvulsive therapy, schizophrenia, bipolar disorder

ÖZ

Amaç: EKT uygulaması ile, TSP-1 ekspresyonunun arttığına ve TSP-1 ile sinaptojenik etki arasında ilişki olduğuna yönelik kanıtlar artmıştır. Çalışmamızda, TSP-1 ile EKT etki mekanizması arasındaki olası bağlantıyı saptamak ve şizofreni ve bipolar bozukluk hastaları ile kontrol grubunu TSP-1 düzeyleri açısından karşılaştırmayı amaçladık.

Yöntemler: Bipolar bozukluk ve şizofreni tanısıyla hastanede yatarak tedavi gören ve EKT uygulaması planlanan, 20 şizofreni akut alevlenme ve 10 bipolar bozukluk manik epizod tanılı erkek hasta ile, cinsiyet ve yaşça hastalarla eşleştirilmiş 28 sağlıklı gönüllü çalışmaya alındı.

Bulgular: Serum TSP-1 düzeyi sağlıklı grupta hasta grubuna göre anlamlı olarak yüksek olarak saptandı. Serum TSP-1 düzeyi, EKT sonrasında kontrol grubuna göre anlamlı farklılık göstermedi. Hastaların serum TSP-1 düzeyleri, EKT sonrasında, öncesine göre anlamlı farklılık göstermedi. Laboratuvar ve klinik bulgularla serum TSP-1 düzeyleri arasında anlamlı korelasyon saptanmadı.

Sonuç: Şizofreni ve bipolar bozukluk tanılı hastalarda, serum TSP-1 düzeylerinin kontrol grubuna göre anlamlı düşüklüğünün EKT sonrasında ortadan kalkması, hastalıkların etiyolojisinde ve EKT uygulamasında TSP-1 molekülünün rol alabileceğini düşündürmektedir.

Anahtar Kelimeler: Trombospondin-1, Elektrokonvülzif terapi, Bipolar Bozukluk, Şizofreni

Our article is an excerpt from medical specialty thesis of Hicret Kan who is one of the authors.

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INTRODUCTION

Bipolar disorder (BD) is a chronic disease that is described by recurrent manic, depressive, or mixed episodes with no specific order, where the person may recover a completely healthy mood between these periods.[1] Schizophrenia is a chronic mental illness that usually begins in adolescence or early adulthood, is defined by disturbances in thought, emotion, and behavior, in which the functionality is significantly impaired, the cause of which is not clearly understood, and has different clinical manifestations.[2]

There is a growing opinion that schizophrenia and BD, which are conceptualized as different diseases, share the same spectrum and are similar in many ways.[3] Although the molecular and cellular pathology of these disorders has not yet been elucidated, synaptic and dendritic changes have been reported in both diseases.[4,5] Recent studies have shown that losses of astroglial cells occur in schizophrenia and BD and are associated with neuronal changes.[6,7]

TSP-1 is an extracellular matrix protein derived from astrocytes that promote synaptogenesis.[8] The release of TSP-1 from astrocytes has been demonstrated to be altered in some neurodevelopmental and neurodegenerative diseases due to synaptic and dendritic changes which may be reversed by the addition of TSP-1.[9,10] Although there are limited data on the role of TSP-1 in schizophrenia, some polymorphisms in the TSP-1 gene have been identified as associated with a risk of schizophrenia, and a post-mortem study showed a significant decrease in TSP expression in the anterior cingulate cortex of schizophrenic patients.[11,12]

Electroconvulsive therapy is one of the oldest methods of biological treatment based on the principle of inducing a grand mal epileptic seizure through external electrical stimulation of the brain. Various psychiatric and neurological disorders such as psychotic depression, risk of suicide, schizophrenia with catatonic excitement, manic excitement not responding to treatment, delirium, and neuroleptic malignant syndrome are the primary indications of electroconvulsive therapy (ECT).[13] While it is not clear how ECT exerts its therapeutic efficacy in the brain, its neuroplastic effects have recently been addressed.[14] In a recent study, we showed that there may be a relationship between ECT and the Glial cell line-derived neurotrophic factor (GDNF) molecule.[15]

In the only study on the relationship between ECT and TSP-1, the effect of ECT seizures on the expression of TSP in the mouse hippocampus was investigated and the expression of TSP-1 and glial fibrillary acid protein (GFAP) was found to increase the following repeated applications of ECT. It was concluded that repetitive ECT applications regulate the expression of TSP-1 by the activation of astrocytes and that the synaptogenic effect of ECT is likely related to TSP-1.[16]

Our study focused on the functions of TSP-1 in the effect of ECT on patients' clinical improvement. Another aim of the study is to compare the level of TSP-1 in BD and schizophrenia, which are chronic psychiatric diseases with changes in cerebral volume and neurodegeneration, with healthy controls. Our assumptions are that following the repeated applications of ECT, levels of TSP-1 will increase relative to pre-treatment and TSP-1 levels will be lower in patients with chronic psychiatric disease compared to control group.

MAIN POINTS

- TSP-1 levels of patients were significantly lower than controls.
- TSP-1 might have a role in the etiology of these disorders.
- TSP-1 might have a role also in the mechanism of electroconvulsive therapy.

METHODS

Subjects

Male patients who were considered eligible to be received at the Bakırköy Prof Dr Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, diagnosed with BD or schizophrenia as per the DSM-5 diagnostic criteria and were considered for ECT, were included in the study. To exclude the possible effects of women-specific hormonal changes on TSP-1 from being a confounding factor, our study group consisted solely of male patients. Of the patients admitted to the hospital from July 2016 to December 2016 and referred to the ECT, 20 patients diagnosed with acute schizophrenia episode and 10 patients with manic episodes of BD who met the inclusion and exclusion criteria and a control group consisting of 28 healthy individuals participated in the study. The healthy group comprised volunteers who were considered healthy at the psychiatric interview and who were matched to the group of patients by gender and age.

Exclusion Criteria

The patients with the following criteria were excluded:

- Presence of psychiatric disorders due to intellectual disability, dementia, or general medical condition,
- alcohol-substance use disorder,
- psychiatric disorder in the first-degree relatives of the healthy control group,

- medical conditions affecting the neurological or another system, and
- early termination of ECT therapy for any reason.

Procedure

The form with socio-demographic questions was filled in by the psychiatrists. The Young Mania Rating Scale (YMRS) has been applied in patients with manic episodes of BD, and the positive and negative syndrome (PANSS) scale was applied to schizophrenic patients for assessing the patients prior to and after ECT.

Blood was collected from patients included in the study before beginning ECT treatment and after the last ECT session (2 times) and from healthy controls (once) in tubes after fasting for 8 hours or more. The samples taken were transferred to the laboratory under +4°C conditions and rotated at 4000 g for 5 minutes. Separated serum specimens were transferred into Eppendorf tubes and stored at −80°C.

The YMRS was developed to evaluate the manic state.[17] It is filled in by the psychiatrists. The validity and reliability study was conducted in our country.[18] Positive and negative syndrome scale is a semistructured interviewing scale improved and composed of 30 items and 7-point severity assessment.[19] The reliability and validity study was carried out in our study.[20]

Measuring the Levels of Thrombospondin-1

To summarize, the method is based on the basis of quantitative measurement of TSP-1 concentration in human serum samples using a colorimetric spectrophotometer in vitro. A graph was acquired with the optical density of the standards to verify the study and determine the concentrations of TSP-1 in the human serum samples analyzed. The samples tested were calculated in ng/mL based on the resulting standard curve and suggested formula. The detection range of the kit ranges from 7.81 to 500 ng/mL. TSP-1 levels of patient group before and after ECT as well as TSP-1 levels of healthy controls were calculated by enzyme-linked immunosorbent assay procedure.

Ethical Principles

The approval of the ethics committee for the thesis was received from Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee decision number 2016/07/04 and dated June 15, 2016. Participants were briefed on the study and asked to read and complete the informed consent form.

Data-Analysis

Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA) was worked out for statistical analysis. While assessing the study results, the categorical variables were given as a percentage and the continuous variables as the mean ± standard deviation. Chi-square test was used to compare categorical variables. The normal distribution was evaluated using the Kolmogorov–Smirnov assay. Student's *t*-test was used for parametric values, and the Mann–Whitney *U* test was used for paired groups' comparison of non-parametric continuous variables. Continuous variables before and after therapy were compared with the *t*-test in dependent groups. Pearson and Spearman's correlation analyses were used to assess for clinic and laboratory variables. The statistical significance was agreed as $P < .05$.

RESULTS

The study sample consisted of 30 patients and 28 healthy controls, and in the patient group, 20 patients (66.7%) were diagnosed with schizophrenia and 10 patients with BD manic episode (33.3%). Sociodemographic features of the groups are shown in Table 1. The mean PANSS scores in patients with schizophrenia before and after ECT were 121.40 ± 9.54 and 73.55 ± 9.65, respectively, and the mean YMRS scores in patients with BD before and after ECT were 46.90 ± 5.02 and 2.10 ± 1.40, respectively.

When the pre-and post-ECT concentrations of TSP-1 in the patients were compared, the mean TSP-1 level was found to be 97.87 ± 83.55 ng/mL before ECT and 105.80 ± 60.68 ng/mL after ECT. While the level of TSP-1 increased after ECT compared to before, no statistically

Table 1. Characteristic of Groups

	MPD (N = 30)	HC (N= 28)	Statistics
Sex			
Male, n (%)	30 (100)	28 (100)	
Female, n (%)	0 (0)	0 (0)	
Smokers, n (%)	16 (53.3)	16 (57.1)	$\chi^2 = 0.085$, $P = .771$
Age; mean ± SD[2] (years)	36.27 ± 9.77	36.64 ± 9.33	$t = -0.150$, $P = .882$
Education level; mean± SD (years)	8.23±4.07	12.57±3.97	$t = -4.099$, $P < .001$

mean ± SD = mean ± standard deviation.
MPD, major psychiatric disorder; HC, healthy controls; χ^2, chi-square test value; *t*, Student's *t* test.

significant difference was observed between the 2 periods ($P=.360$). The mean concentration of TSP-1 for the control group was 178.15 ± 139.87 ng/mL. Compared to the group of patients prior to ECT, the level of TSP-1 was significantly higher in the control group ($P=.008$). When TSP-1 levels in the patient group and controls were compared after ECT, no significant differences were seen ($P=.116$) (Table 2) (Figure 1). In addition, a correlation was not established between TSP-1 levels and clinical or laboratory parameters (number of hospitalization, duration of psychiatric illness, mean PANSS scores, mean YMRS scores, number of ECT sessions ($P > .05$).

DISCUSSION

Serum TSP-1 levels prior to and after ECT in schizophrenia and BD, which are chronic psychiatric diseases, were compared to healthy controls and the function of TSP-1 was investigated.

The primary outcome of our study was that serum TSP-1 levels were significantly lower in pre-treatment patients compared to healthy controls. Following repeated applications of ECT, serum levels of TSP-1 increased and the significant difference from the control group disappeared.

There is a growing opinion that schizophrenia and BD, which are conceptualized as different diseases, share the same spectrum and are similar in many ways.[4] Schizophrenia and BD are highly clustered together in families, and numerous susceptibility loci have been reported to be common in genome-wide association studies.[21] Aside from genetics, the overlapping symptoms in the clinic of both diseases are rather common. Psychosis, depression, anxiety, sleep disorders, and various disorders of cognitive functions are detected in BD, and the distinction between these symptoms and schizophrenia cannot be made through defined boundaries.[22]

There is growing evidence that schizophrenia and BD are associated with neurodegeneration, cognitive impairment, and cortical atrophy.[23-25] Recently, synaptic and dendritic changes in the pathophysiology of schizophrenia and BD have been emphasized. Synaptic control is an important function of extracellular matrix (ESM). Many ESM molecules work together to regulate synaptogenesis, neuroplasticity, and homeostasis. The key to these functions lies in the close interactions between ESM and astroglial and neuronal elements.[26] In schizophrenia, a decrement in the volume, number, and density of astroglial cells was observed in many regions of the brain, and there is a decrement in the mRNA levels of the astrocyte marker glial fibrillary acid protein.[27] Indeed, an abnormality in synaptic functions and a decrease in synaptic density were observed in both diseases.[28-30] However, electron microscopy studies in schizophrenia showed a significant reduction in dendritic projections in areas covering various cortical regions, including the prefrontal and auditory cortical region.[31] Similarly, there has been evidence of decreased density of dendritic protrusions in the dorsolateral prefrontal cortex and hippocampus in BD.[32]

Table 2. Comparison of Serum Thrombospondin-1 Levels

	Trombospondin-1 Levels	Statistics
Before ECT (patients)	97.87 ± 83.55	$z=0.915$, $P=.360$
After ECT (patients)	105.80 ± 60.68	
Healthy control	178.15 ± 139.87	$z=-2.645$, $P=.008$**
Before ECT (patients)	97.87 ± 83.55	
Healthy control	178.15 ± 139.87	$z=-1.572$, $P=.116$
After ECT (patients)	105.80 ± 60.68	

z, Mann–Whitney *U*.

It has been reported that TSP-1, an ESM molecule secreted from astrocytes, can regulate synaptogenesis through receptor α2δ-1 and neuroligin-1, promote the proliferation and differentiation of neural progenitor cells, and play a role in synaptic remodeling after cerebral ischemia.[8,33,34] In addition, in some neurodevelopmental and neurodegenerative diseases such as Down syndrome, Fragile X syndrome, and Alzheimer's disease, it has been shown that TSP-1 release from astrocytes is disrupted, this situation is associated with synaptic and dendritic alterations and these changes can be reversed with the addition of TSP-1.[9,10] Although there are limited data on the function of TSP-1 in schizophrenia, some polymorphisms in the TSP-1 gene have been identified as associated with a risk of schizophrenia, and a post-mortem study showed a significant decrement in TSP expression in the anterior cingulate cortex of schizophrenic patients.[11,12]

In line with our hypothesis, one of the primary outcomes of our study is that in BD and schizophrenia, which are chronic psychiatric illnesses with neurodegeneration, pre-treatment serum levels of TSP-1 are significantly lower than in healthy controls. This result suggests that TSP-1 could function in the etiology of BD and schizophrenia.

Electroconvulsive therapy has been a method of treatment for many years due to its efficacy in various psychiatric diseases such as treatment-resistant BD, major depression, and schizophrenia, and its fast-acting effects.[35,36] However, the mechanism of ECT remains uncertain. Recently, a focus was placed on the neuroplastic effects of ECT. In many studies, ECT has been reported to cause a marked increase in hippocampus and amygdala volume and cortical thickness.[37,38] In addition, there is growing

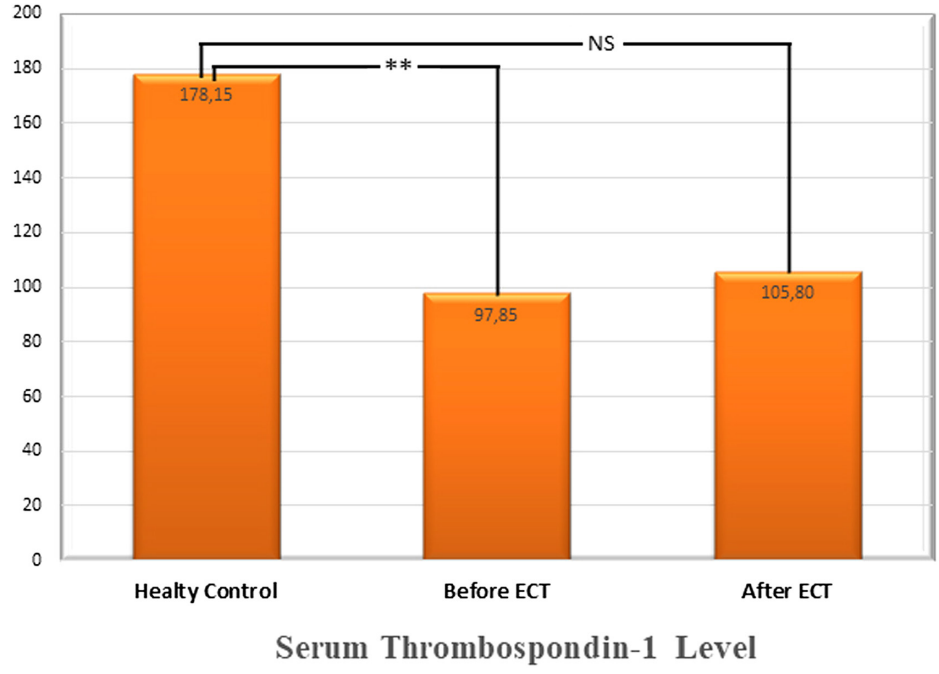


Figure 1. Serum thrombospondin-1 levels. $^{**}P \leq .05$; NS, non-significant; ECT, electroconvulsive therapy.

evidence that ECT initiates synaptic re-organization and increases synaptogenesis and neurogenesis.[39]

We are not aware of any clinical studies that examine the relationship between ECT and TSP-1 in patients with BD and schizophrenia. In the sole literature study examining the effect of ECT on the level of TSP-1, the effect of ECT seizures on the expression of TSP in the mouse hippocampus was investigated and the expression of TSP-1 and GFAP proteins was found to increase following repeated applications of ECT. In this study, it was concluded that repetitive ECT applications regulate the expression of TSP-1 by activation of astrocytes and that the synaptogenesis effect of ECT is likely related to TSP-1.[16]

One of the key findings of our study, consistent with the aforementioned literature, is the increase in serum TSP-1 concentrations in the post-ECT group of patients relative to pre-treatment. However, this increase is not statistically significant. This may be due to different degrees of possible neurodegeneration because the group of patients is limited in number and the group is not homogeneous in terms of diagnosis and duration of the disease.

Another key outcome of our study was the lack of significant difference between post-ECT serum TSP-1 levels in the patient group and the control group. Following repeated applications of ECT, serum levels of TSP-1 increased and the significant difference from the control group disappeared. This result suggests that TSP-1 may have a function in the mechanism of action of ECT. In addition, this result suggests that ECT may have positive effects on the increase in synaptogenesis in patients with BD and schizophrenia and lead to similar limits in healthy people via TSP-1.

As far as we know, no studies have been published on the effect of antipsychotics on thrombospondins. The fact that all patients in our study received antipsychotic therapy with ECT and we were not able to standardize the antipsychotics used may have affected our results.

This study has a few limitations. The reason we included only male patients in our study group is to exclude the potential effects of women-specific hormonal changes on the level of TSP-1 from being a confounding factor. Furthermore, a study group made up solely of male patients may not be representative of the general population. One of the limitations of this study is the small sample and the patient group is not homogenous in terms of the diagnosis and duration of the disease. The inclusion of only patients in the manic phase in our study may not reflect the population of BD. Moreover, the possible effect of antipsychotics on the level of TSP-1 could not be ruled out because all patients received ECT as consolidation therapy together with antipsychotic therapy and we could not standardize the antipsychotic drugs used.

CONCLUSION

To better understand the function of TSP-1 in the effect of ECT on the clinical improvement of patients, more studies representing the entire patient population, including female patients, consisting of patients in

all 3 periods that enable us to evaluate the effects of episodic nature of BD are needed. Additionally, to exclude possible effects of antipsychotics on TSP-1, including a group that received only ECT in the study would be beneficial in clarifying the effect of ECT on TSP-1.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Date: June 15, 2016, Decision No: 2016/07/04).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.K.; Design – N.K.; Supervision – T.K.; Data Collection and/or Processing – M.A.; Analysis and/or Interpretation – T.K.; Literature Search – M.A.; Writing Manuscript – H.K.; Critical Review – H.K.

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